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PATENTS
Case 26890-CIP

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of :

Jacob Berger et al. :

Application No. 07/704,565 : Group Art (not yet known)

Filed May 22, 1991 : Examiner (not yet known)

For TRICYCLIC 5-HT_3 RECEPTOR ANTAGONISTS

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

INFORMATION DISCLOSURE STATEMENT

In compliance with 37 CFR 1.56, 1.97 & 1.98, Applicants direct the attention of the Office to the following documents, listed on the attached Form PTO-1449, which may be material to the examination of this application.

The Lancet, **September 23, 1989**, Page 717 **(Lancet)**

Lancet, discussed on pages 1 and 2 of the application, describes the use of 5-HT_3 antagonists as antipsychotic agents, cognition enhancing agents, anxiolytic agents, and in treating dependency disorders. Lancet also describes the anti-emetic activity of 5-HT_3 antagonists such as ICS 205-930 (tropisetron), ondansetron, and granisetron.

Gastroenterology Clinics of North America, **1989**, *18*, 437 **(Reynolds)**

Reynolds, discussed on page 2 of the application, describes the prokinetic activity of cisapride a 5-HT_3 receptor antagonist.

Trends. Pharmacol. Sci., **1988**, *9*, 141 **(Peatfield)**

Peatfield, discussed on page 2 of the application, describes the use of the 5-HT_3 antgonist MDL-72222 in treating migraine.

J. Pharmacol. Exp. Ther., **1988**, *245*, 773 **(Scholtysik et al.)**

Scholtysik et al., discussed on pages 2 and 3 of the application, describes the class I and class II antiarrhythmic properties of the 5-HT_3 antagonist ICS 205-930.

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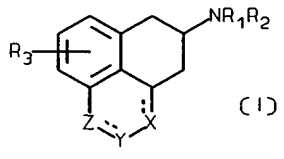
PCT Application Publication No. WO 88/04292 **(Szmuszkovicz)**

Szmuszkovicz discloses compounds of Formula I:



(I)

in which:

a dashed line denotes an optional bond;

X is CHR_5, Y is CR_5 or C=O, and Z is NR_4; or

X and Z are CHR_5 and Y is NR_4; or

Y and Z are CHR_5 and X is NR_4;

R_1 and R_2 are hydrogen, C_{1-3} alkyl or C_{1-4} alkyl, with the proviso that when R_2 is C_{1-4} alkyl R_1 is hydrogen; or

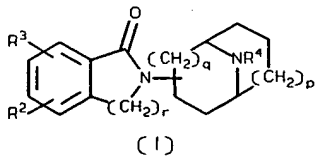
NR_1R_2 is azetidinyl, pyrrolidinyl, piperidinyl or morpholinyl;

R_3 is hydrogen, fluoro, chloro, bromo, C_{1-3} alkyl, C_{1-3} alkoxy, trifluoromethyl, C_{1-3} alkylcarbonyloxy, phenylcarbonyloxy or benzylcarbonyloxy; and

R_4 is part of a double bond when the optional bond is present or is hydrogen C_{1-3} alkyl or $C(O)R_6$ wherein R_6 is C_{1-3} alkyl or benzyl; and the acid addition salts and use (i.e., in treating psychotic behavior) thereof.

European Patent Application Publication No. 0 093 488 **(Hadley)**

Hadley discloses dopamine receptor antagonists of Formula I:



(I)

in which:

r is 1 or 2;

p and q are independently 0 to 2;

R_2 and R_3 can be independently selected from, *inter alia*, hydrogen, halogen, C_{1-6} alkyl, amino and aminocarbonyl; and

R_4 can be, *inter alia*, C_{1-7} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl-C_{1-2} alkyl, or a group $(CH_2)_tR_7$

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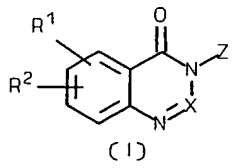
where t is 1 or 2 and R_7 is thienyl, or is phenyl optionally substituted by one or two substituents selected from C_{1-4} alkoxy, trifluoromethyl, halogen, carboxy, esterified carboxy, or C_{1-4} alkyl further optionally substituted by hydroxy, C_{1-4} alkoxy, *in vivo*, hydrolysable acyloxy, carboxy, or esterified carboxy; and the enantiomers, racemates, compositions, pharmaceutically acceptable salts, solvates, *N*-oxide derivatives, processes for preparation, and uses (i.e., in treating emesis, impaired gastro-intestinal motility, and CNS disorders) thereof.

U.S. Patent No. 4,959,367 **(King)**

King discloses 5-HT receptor antagonists of Formula I:



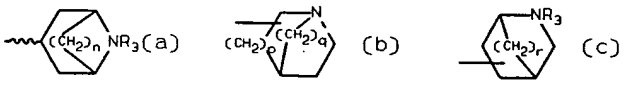
(I)

in which:

X is CH or N, preferably N;

R_1 and R_2 can be independently selected from, *inter alia*, hydrogen, halogen, C_{1-6} alkyl, amino, amino carbonyl, (C_{1-7} acyl)amino, (C_{1-6} alkyl)amino, and di(C_{1-6} alkyl)amino; and

Z is a group selected from Formula (a), (b) or (c):



in which:

n is 2 or 3;

p is 1 or 2;

q and r are 1 to 3; and

R_3 and R_4 are C_{1-4} alkyl; and the enantiomers, racemates, compositions, pharmaceutically acceptable salts, solvates, *N*-oxide derivatives, processes for preparation, and uses (i.e., in treating migraine, cluster headaches, trigeminal neuralgia, visceral pain, arrhythmia, obesity, emesis, CNS disorders, and gastrointestinal disorders) thereof.

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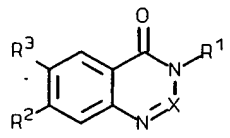
J. Med. Chem., **1990**, *33*, 2942-2944 **(Salituro et al.)**

Salituro et al discloses compounds of the generic formula:



in which:

X is CH or N;

R_2 is hydrogen, amino or nitro;

R_3 is hydrogen or chloro, and

R_1 is *endo*-8-methyl-8-azabicyclo[3.2.1]oct-3-yl or (±)-1-azabicyclo[2.2.2]oct-3-yl; and the processes for preparation thereof; and reports substantial loss in 5-HT_3 receptor antagonist activity when X is CH.

The following references were cited by the Examiner during prosecution of the parent application (Application No. 07/442,082), filed November 28, 1989:

U.S. Patent No. 4,309,543 **(Keeley)**

U.S. Patent No. 3,896,132 **(Bernauer et al.)**

U.S. Patent No. 3,341,528 **(Shavel et al.)**

Keeley, Bernauer et al., and Shavel et al. were cited as examples of other and material different processes by which the compounds of the invention could be made in support of a restriction requirement between claims to compounds and claims to the process of making the compounds.

U.S. Patent No. 4,571,396 **(Hutt et al.)**

Hutt et al. was listed by the Examiner on the Notice of References cited but not referred to in the text of the Examiner's explanation.

Chemical Abstracts, **1978**, *89*:100352x **(Komatsu et al.)**

Chemical Abstracts, **1988**, *108*:221716p **(Hilbert et al.)**

Komatsu et al. and Hilbert et al. were cited as examples of methods for treating gastro-intestinal disorders and CNS disorders, respectively, in support of a rejection of a generic claim to methods of use as an improper Markush grouping.

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Copies of the above documents are provided herewith. The Examiner is requested to consider these documents, and to indicate that this has been done by signing and returning a copy of the Form PTO-1449.

Respectfully submitted,

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September 10, 1991
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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on Sep. 10, 1991
(Date of Deposit)

Wayne W. Montgomery P-35,016
Name of applicant, assignee or Registered Rep.

Wayne W. Montgomery 9/10/91
Signature Date